UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/442,277	05/16/95	BOYSE E	6287-026

HM22/0814

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EXAMINER	
WITZ,J	
ART UNIT	**PAPER NUMBER**
1651	21

DATE MAILED: 08/14/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/442,277	Applicant(s) BOYSE ET AL.	
	Examiner Jean C. Witz	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *60-62,67-102 and 104-111* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *60-62,67-102 and 104-111* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *18* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Arguments

1. Applicant's arguments with respect to the claims of record have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

2. Claims 60-62, 67-102 and 104-111 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of providing hematopoietic reconstitution of a human patient comprising 1) treating the patient to destroy the patient's endogenous hematopoeitic stem cell population, and 3) introducing into the patient a therapeutically effective amount of the expanded human neonatal or fetal hematopoeitic stem cells obtained from umbilical cord or placental blood, does not reasonably provide enablement for the method of treating a human patient as currently claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The currently claimed invention recites a method for treating a human patient in need of hematopoietic stem cell function by growing in vitro human neonatal or fetal hematopoietic stem cells obtained from circulating human neonatal or fetal blood and introducing into the patient a therapeutic composition of the expanded stem cells to provide hematopoietic stem cell function.

First, it is noted that Applicants' invention is drawn to the discovery of the presence of hematopoietic stem cells in umbilical cord blood and placental blood in amounts sufficient to provide hematopoietic reconstitution to a human patient who has had his/her endogenous hematopoeitic stem cell population. The current claims recite an invention that is broader than the disclosed invention and therefore is not enabled for the following reasons.

First, it is not clear what is meant by the term "hematopoietic stem cell function". The specification defines stem cells as having extensive self-renewal or self-maintenance capacity as well as being capable of differentiation into several sublines of progenitor cells. The specification states that "[s]ome of the stem cells differentiate upon need, but some stem cells or their daughter cells produce other stem cells to maintain the precious pool of these cells. Thus, in addition to maintaining their own kind, pluripotential stem cells are capable of differentiation into several sublines of progenitor cells with more limited self-renewal capacity or no self-renewal capacity." As is stated by the specification, stem cells are defined functionally, i.e. by what they do, rather than morphologically, i.e. by what they look like. As a result of this definition, it is clear from the disclosure that stem cells are not a static entity, but in fact the quality of being a stem cell, or "stemness", as is used in the specification , may change through the life and reproductive history of one particular cell, where a stem cell which differentiates becomes a progenitor and loses its self-renewal capability. The specification states that "[t]he stem cell and progenitor cell compartments are themselves heterogeneous with varying degrees of self-renewal or proliferative

capacities." Further, the specification indicates that "[s]elf-renewal would appear to be greater in those stem cells with the shortest history of cell division, and this self-renewal would become progressively more limited with subsequent division of the cells."

Therefore, a stem cell's "function" is to undergo mitosis and alternatively to undergo differentiation. However, there is a large degree of unpredictability as to any other effects and functions of stem cells as they undergo mitosis and differentiation as part of the physiological functioning of the body, including the manipulation of the stem cells in a method of gene therapy. Since Applicants have shown only hematopoietic reconstitution, Applicants claims should be so limited.

Further, Applicants provide showings and disclosures that indicate hematopoietic reconstitution after destruction of the endogenous hematopoietic stem cells of the patient. The diseases and conditions listed as treatable in the specification either require the destruction of the hematopoietic stem cells because of malignancy or malfunction or the destruction is a by-product of collateral treatment for another malignancy or condition suffered by the patient. Applicants have not shown, and in fact emphasize in the response, that the hematopoietic stem cells of the invention engage in long term reconstitution. In view of the statements made in the response with regard to the Ende reference, which discloses the administration of umbilical cord blood without destruction of the endogenous hematopoietic stem cell population of the patient, there is unpredictability and in fact, Applicants argue that it would not be expected by one skilled in the art that engraftment would occur. Therefore, Applicants claims should be limited

to the conditions under which engraftment occurred which requires the destruction of the endogenous stem cell population of the patient to be treated.

Finally, since there is no way to visually identify a stem cell, the only way to know that stem cells existed in a cell sample is to assay for the presence of identifiable progenitors that develop from a cell sample that did not contain the identifiable progenitors previously. To identify or assay for the presence of stem cells, the specification states that:

> "These progenitor and stem cells have been detected and assayed for by placing dispersed suspensions of these cells into mice, and noting those cells that seeded to an organ such as the spleen and which found the environment conducive to proliferation and differentiation. These cells have also been quantified by immobilizing the cells outside of the body in culture plates (in vitro) in a semi-solid support medium such as agar, methylcellulose, or plasma clot in the presence of culture medium and certain defined biomolecules or cell populations which produce and release these molecules. Under the appropriate growth conditions, the stem or progenitor cells will go through a catenated sequence of proliferation and differentiation yielding mature end stage progeny, which thus allows the determination of the cell type giving rise to the colony. If the colony contains granulocytes, macrophages, erythrocytes, and megakaryocytes (the precursors to platelets), then the cell giving rise to them would have been a pluripotential cell. To determine if these cells have self-renewal capacities, or stemness, and can thus produce more of their own kind, cells from these colonies can be replated in vivo or in vitro. Those colonies which upon replating into secondary culture plates, give rise to more colonies containing cells of multilineages, would have contained cells with some degree of stemness."

As the claims presently are interpreted, the stem cells need only be derived from fetal or neonatal blood. The term "fetal" means "pertaining to, involving or characteristic of a fetus" and the term "fetus" means "the unborn offspring of viviparous mammals in the later stages of development: in human beings, from about the beginning of the ninth week after fertilization." The term "neonatal" means "pertaining to the neonate" and the term "neonate" means "a newborn infant; specifically, an infant from birth through its 28th day." Therefore, the scope of Applicants' claims include stem cells obtained from a fetus beginning at the ninth week after fertilization and stem cells obtained from an infant of 28 days of age. However, Applicants have not shown collection, expansion or use of these stem cells. Applicants' disclosure is limited to the collection, expansion and use of stem cells obtained from umbilical cord and placental blood. It remains unpredictable that fetal stem cells from a nine-week old fetus would be capable of engaging in both the mitotic function and the differentiative functions required by a human adult as a result of such a transplant or that sufficient numbers could be collected. Applicants repeatedly emphasize the unpredictability of the art of stem cell identification and use. Therefore, claims should be limited in scope with the showing of the specification.

Finally, claim 60 requires the introduction of a composition containing a cryoprotective agent and stem cells. It is unclear as to the purpose of the cryoprotective agent with regard to the method of treating the patient. The cryoprotective agent is not part of the therapy, and therefore claims for such are not enabled by the specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jean C. Witz whose telephone number is (703) 308-3073. The examiner can normally be reached on 6:30 a.m. to 4:00 p.m. M-Th and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (703) 308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Jean C. Witz
Primary Examiner
Art Unit 1651

August 13, 2001